UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/722,587	11/28/2003	Robert D. Rosenberg	P-6170-US	5678

49443 7590 03/02/2011

Pearl Cohen Zedek Latzer, LLP
1500 Broadway
12th Floor
New York, NY 10036

EXAMINER	
GOON, SCARLETT Y	

ART UNIT	PAPER NUMBER
1623	

NOTIFICATION DATE	DELIVERY MODE
03/02/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

USPTO@pczlaw.com
Arch-USPTO@pczlaw.com

Office Action Summary	Application No.	Applicant(s)	
	10/722,587	ROSENBERG ET AL.	
	Examiner	Art Unit	
	SCARLETT GOON	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 January 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7-38,40-44 and 46-71* is/are pending in the application.

4a) Of the above claim(s) *3-5,7,9,19,21,32-38,40-42,44,49-62,64 and 65* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2, 8, 10-18, 20, 22-31, 43, 46-48, 63 and 66-71* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 26 January 2011 has been entered.

DETAILED ACTION

This Office Action is in response to Applicants' Remarks filed on 26 January 2011. Claims 6, 39 and 45 were previously cancelled. **No amendment to the claims was submitted.**

Claims 1-5, 7-38, 40-44 and 46-71 are pending in the instant application.

Claims 3-5, 19, 21, 32-38, 40, 41, 49-62, 64 and 65 were previously withdrawn from further consideration in the Office Action dated 8 December 2008 pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention and/or nonelected species, there being no allowable generic or linking claim.

Claims 7, 9, 42 and 44 are withdrawn from further consideration in the Office Action dated 15 September 2009 pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim.

Claims 1, 2, 8, 10-18, 20, 22-31, 43, 46-48, 63 and 66-71 are examined on the merits herein.

Priority

This application claims priority to U.S. provisional application no. 60/429,946 filed on 27 November 2002 and U.S. provisional application no. 60/456,889 filed on 21 March 2003.

Claim Objections

Claim 66 is objected to because of the following informalities: The claim has a status identifier of "previously presented." However, the claim shows amendments in which the recitation "is enzymatic only and" has been struck out. This amendment was made in the claims filed on 6 July 2010. Thus, the recitation "~~is enzymatic only and~~" should be deleted in the instantly examined claim set as it was presented in a previously filed claim set. Appropriate correction is required.

The following rejections of record in the previous Office Action are maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Section [0001]

Claims 1, 2, 8, 10-18, 20, 22-31, 46, 47 and 67-70 are rejected under 35 U.S.C. 103(a) as being unpatentable over journal article publication by Pikas (IDS dated 26 December 2006), in view of journal article publication by Habuchi *et al.* (of record), in view of journal article publication by Koeller *et al.* (of record), in view of journal article publication by Toone *et al.* (of record), in view of journal article publication by Pettersson *et al.* (of record), in view of journal article publication by Kobayashi *et al.* (of record).

Pikas teaches enzymes involved in the biosynthesis and degradation of heparin-related polysaccharides, namely heparanase, which degrades heparin and heparan sulfate, and N-deacetylase/N-sulfotransferase (NDST), which generates the complex structure of heparin and heparan sulfate. In determining the substrate recognition properties of heparanase, Pikas modified a polysaccharide obtained from the K5 strain of *Escherichia coli* having the structure $(GlcA\beta1\text{-}4GlcNAc\alpha1\text{-}4)_n$ (p. 306, column 1, C-2). This K5 polysaccharide is identical to the unmodified parts of heparin sulfate. The K5 polysaccharide was modified in a controlled stepwise fashion by combining different treatments; (1) chemical *N*-deacetylation and *N*-sulfation, (2) enzymatic GlcA C5-epimerization and (3) chemical O-sulfation.

The teachings of Pikas differ from that of the instantly claimed invention in that O-sulfation of the polysaccharide was accomplished chemically rather than enzymatically.

Habuchi *et al.* teach that various enzymes participating in the biosynthesis of heparan sulfate have been purified to homogeneity and cloned (p. 65, paragraph 2). Studies of the heparan sulfate enzymes offered new information regarding the specificity of the enzymes, and further confirmed the biosynthetic process as depicted in Figure 1. (p. 69). As indicated, the biosynthesis of heparan sulfate depends on multiple glycotransferases, sulfotransferases, and an epimerase. Most of these enzymes that participate in heparan sulfate biosynthesis have been purified and molecularly cloned, including *N*-deacetylase/*N*-sulfotransferases, 3-*O*-sulfotransferases, 6-*O*-sulfotransferses, a 2-*O*-sulfotransferase, and an epimerase (entire article; p. 71, Table II). *N*-deacetylase/*N*-sulfotransferase is a bifunctional enzyme responsible for N-

deacylating the GlcNAc unit followed by *N*-sulfation of the resulting amino group (p. 70-72, section E-2-1). Enzymes of this subfamily differ in the extent of *N*-sulfation. The 3-*O*-sulfotransferases, 6-*O*-sulfotransferases and 2-*O*-sulfotransferase catalyze the transfer of a sulfate group from PAPS to the corresponding position on the heparin chain. Although the 2-*O*-sulfotransferase generally only catalyzes the transfer of a sulfate group to C-2 of an iduronic acid residue, C-2 sulfation of GlcA may occur during a transient period after *N*-deacetylation/*N*-sulfation of GlcNAc and before epimerization of GlcA (p. 74, first full paragraph). Glucuronyl C5-epimerase catalyzes the conversion of D-glucuronic acid to L-iduronic acid units (p. 69-70, section E-1). The glucuronyl C5-epimerase requires preceding *N*-sulfation of the neighboring *N*-acetylglucosamine.

Koeller *et al.* teach complex carbohydrate synthesis tools for glycobiologists. Complex carbohydrate and glycoconjugate synthesis, such as the heparin pentasaccharide repeating unit for anti-coagulant acitivty (Figure 1), remains much more complicated than that of other biomolecules (p. 1158, column 1, first paragraph). However, enzyme-based strategies toward complex glycoconjugates are an emerging technology that has the great potential to greatly simplify glycan assembly. Koeller *et al.* teach that the application of enzymes to organic synthesis is a particularly powerful approach, and in some cases a single enzymatic transformation can be substituted in place of numerous sequential chemical reactions (p. 1158, paragraph bridging two columns). In the case of complex oligosaccharide synthesis, the enzymatic approach is especially noteworthy for glycosidic bond formation. Such enzymatic techniques have greatly simplified the synthesis of carbohydrate-based structures and enzymatic

methods will gain increased utility as more glycosyltransferases become available and substrate cost decreases (p. 1167, column 1). Koeller *et al.* further teach that post-translational modifications, such as sulfation, phosphorylation, and esterification, are also important additions to glycoconjugate structure (p. 1167, column 1). Future progress in glycobiology will be greatly aided by techniques, such as the disclosed enzymatic synthesis method, that allow facile synthetic access to specific glycoconjugates.

Toone *et al.* teach use of enzymes as catalysts in carbohydrate synthesis. Enzymes offer two major advantages over classical methodologies for the synthesis of carbohydrates (p. 2, first incomplete paragraph). First, enzymes are compatible with aqueous media, which is the most practical medium for synthetic manipulations of unprotected, hydrophilic compounds such as carbohydrates, and therefore avoids the necessity for protection/deprotection schemes (p. 2, first full paragraph). Second, enzyme-catalyzed reactions demonstrate absolute chemospecificity, regiospecificity, and stereospecificity, which is important because carbohydrates generally contain a number of hydroxyl groups of approximately equal reactivity (p. 2, second full paragraph). Therefore, the ability to selectively manipulate a single hydroxyl residue is clearly important.

Pettersson *et al.* teach the purification of a mouse mastocytoma protein required for glucosaminyl *N*-deacetylation and *N*-sulfation. Methods for assaying the activity of *N*-acetylglucosaminyl deacetylase and *N*-deacetylase are further provided (p. 8045, column 1, subheading “Enzyme Assays”).

Kobayashi *et al.* teach the purification and characterization of heparan sulfate 2-sulfotransferase from cultured CHO cells. Methods for the purification of heparan sulfate 2-sulfotransferase from crude extract of CHO cells is further described (p. 7646, column 2). Additionally, methods for assaying the sulfotransferase activity are provided (p. 7646, column 2). The heparan sulfate 2-sulfotransferase was found to exclusively transfer sulfate to the 2-position of L-iduronic acid residue in CDSNS- heparin or EHS tumor heparan sulfate (p. 7651, column 1).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Pikas, concerning the modification of a polysaccharide having the structure $(GlcA\beta1\text{-}4GlcNAc\alpha1\text{-}4)_n$ by chemical *N*-deacetylation and *N*-sulfation, enzymatic GlcA C5-epimerization, and chemical *O*-sulfation, with the teachings of Habuchi *et al.*, regarding the availability and substrate specificity of the different enzymes involved in the biosynthesis of heparan sulfate, with the teachings of Koeller *et al.*, regarding the use of carbohydrate enzymes as a tool for the synthesis of complex carbohydrates, with the teachings of Toone *et al.* regarding enzymes as catalysts in carbohydrate synthesis, with the teachings of Pettersson *et al.*, regarding the purification of a mouse mastocytoma protein required for glucosaminyl *N*-deacetylation and *N*-sulfation, with the teachings of Kobayashi *et al.*, regarding the purification and characterization of a heparan sulfate 2-sulfotransferase from CHO cells. Since Habuchi *et al.* teach that many of the enzymes that participate in heparan sulfate biosynthesis have been purified and molecularly cloned, and that their substrate specificities have been characterized, it would have been *prima facie* obvious for one of

ordinary skill in the art to substitute the chemical modification steps for modification of the polysaccharide disclosed in Pikas (chemical *N*-deacetylation and *N*-sulfation and chemical *O*-sulfation), with enzymatic steps using the enzymes disclosed by Habuchi *et al.* Since Koeller *et al.* teach that the chemical synthesis of complex carbohydrates, such as heparin, is complicated, and that a single enzymatic transformation can be substituted in place of numerous sequential chemical reactions, one of ordinary skill in the art would have been motivated to combine the teachings and substitute enzymatic modifications in place of the chemical modifications. Furthermore, as Koeller *et al.* teach that post-translation modification, such as sulfation or phosphorylation are important additions to glycoconjugate structure, one of ordinary skill in the art would have been motivated to use the sulfotransferase enzymes dislcosed by Habuchi *et al.* in place of the chemical method disclosed by Pikas *et al.*, in order to receive the expected benefit, as disclosed by Toone *et al.*, that the use of enzymes in carbohydrate synthesis is advantageous over classifical methods because enzyme-catalyzed reactions demonstrate absolute chemospecificity, regiospecificity, and stereospecificity, therefore avoiding the necessity for protection/deprotection schemes. In other words, the use of enzymes allows one to have better control over the generated product. Moreover, as Habuchi *et al.* teach that the various enzymes involved in the biosynthesis of heparin/heparan sulfate have been cloned and purified, and Pettersson *et al.* and Kobayashi *et al.* provide various conditions for the various enzymatic procedures, one of ordinary skill in the art would have a reasonable expectation of success in substituting

the use of *N*-acetylglucosaminyl deacetylase/*N*-deacetylase and sulfotransferase enzymes for the chemical steps disclosed by Pikas.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

Response to Arguments

Applicants' arguments, filed 26 January 2011, with respect to the rejection of claims 1, 2, 8, 10-18, 20, 22-31, 46, 47 and 67-70 made under 35 USC § 103(a) as being unpatentable over journal article publication by Pikas, in view of journal article publication by Habuchi *et al.*, in view of journal article publication by Koeller *et al.*, in view of journal article publication by Toone *et al.*, in view of journal article publication by Pettersson *et al.*, in view of journal article publication by Kobayashi *et al.*, have been fully considered but are not persuasive.

Applicants argue that the prior art references, cited alone or in combination, do not teach or suggest the instantly claimed method. Specifically, Applicants state that Pikas teaches a sulfation process that is primarily chemical, and Habuchi *et al.* teach *in vivo* activity of the various enzymes. Additionally, Applicants state that neither Koeller *et al.* nor Toone *et al.* teach the activities of epimerases and O-sulfotransferases. Thus, Applicants argue that since Pikas teaches a reaction that was accomplished chemically, rather than enzymatically, and since neither Habuchi *et al.* nor Pikas do not teach the stepwise enzymatic *in vitro* synthesis of sulfated polysaccharides, nor do Koeller *et al.* and Toone *et al.* describe the activities of epimerases and O-sulfotransferases, claims 1

and 2 are not obvious in view of the disclosed *in vivo* process. Applicants' arguments are the same as that presented in the remarks filed on 6 July 2010 and have been carefully considered again, but are still not found persuasive. Although Pikas teaches chemical synthetic steps, Koeller *et al.* and Toone *et al.* expressly teach that enzymatic reactions are more advantageous than the corresponding chemical reaction because of their simplicity when compared to multi-step chemical reactions. Therefore, since the enzymes involved in the biosynthesis of heparin/heparan sulfate are known, have been cloned and purified, as taught by Habuchi *et al.*, one of ordinary skill in the art would have been motivated to substitute the chemical reaction steps, as taught by Pikas, with enzymatic reactions, as discussed in the rejection above. Furthermore, as Habuchi *et al.* disclose the substrate specificity of each of the known enzymes involved in the biosynthesis of heparin/heparan sulfate, it would have been *prima facie* obvious to one of ordinary skill in the art which substrate is necessary to obtain the desired product. Although Applicants argue that Habuchi *et al.* only disclose *in vivo* steps, Applicants are requested to note that the inclusion of the Habuchi *et al.* reference is to show that bioysnthesis of heparin/heparan sulfate is known in the art, that the enzymes have been cloned and purified, and their substrate specificity determined, thereby allowing one of ordinary skill in the art to use the enzymes for *in vitro* enzymatic synthesis. Furthermore, it is *prima facie* obvious to one of ordinary skill in the art that the teaching of Habuchi *et al.* that these enzymes have been cloned and purified indicates that they could be used for *in vitro* work. Additionally, it is *prima facie* obvious to one of ordinary skill in th art that the characterization of an enzyme's substrate specificity is performed

at the *in vitro* level. As Habuchi *et al.* taught, previous studies of the enzymes provided insight into the biosynthetic process of heparin sulfate. Thus, while Applicants argue that Habuchi *et al.* only disclose the *in vivo* process, one of ordinary skill in the art knows full well that the enzyme activity can be applied at the *in vitro* level, particularly since information regarding the *in vivo* process was obtained at the *in vitro* level. Applicants are also requested to note that the inclusion of Koeller *et al.* and Toone *et al.* is to show why it is more advantageous to use enzymatic reactions instead of chemical reactions in the synthesis of complex carbohydrates, not to explain the activities of epimerases and sulfotransferases, as this was already accomplished in the teachings of Habuchi *et al.* The teachings of Koeller *et al.* that post-translational modifications, such as sulfation, phosphorylation, and esterification, are also recognized as important additions to glycoconjugate structure, combined with the teachings of Toone *et al.* and Koeller *et al.* that the use ofenzymatic reactions is advantageous over chemical reactions in the synthesis of complex carbohydrates, and further coupled with the teachings of the other cited prior art references disclosing the available cloned enzymes as well as their known substrate activity, is sufficient to motivate one of ordinary skill in the art to use enzymes for the synthesis of the structure disclosed by Pikas.

Additionally, Applicants argue that a stepwise, *in vitro*, enzymatic process such as that recited in the claims, is not obvious in view of a corresponding *in vivo* process because *in vitro* synthetic parameters, such as temperature, pH, reaction times, concentration, atmosphere, and ingredients must be carefully selected for each step to work. Thus, Applicant argues that it would not be obvious for a person of ordinary skill

in the art to look at the *in vivo* process described by Habuchi *et al.* to try to perform the *in vitro* process. This argument was also presented in the remarks filed on 6 July 2010 and have been carefully considered again, but are still not found persuasive. Contrary to Applicants' argument that Habuchi *et al.* only teach the *in vivo* process, Habuchi *et al.* expressly disclose the availability of various enzymes involved in the biosynthesis of heparin/heparan sulfate, and properties of the purified and cloned glycosaminoglycan sulfotransferases, including various NDSTs and OSTs (p. 71, Table II). One of ordinary skill in the art would be aware that in order to characterize the substrate specificity of the cloned and purified enzymes as discussed by Habuchi *et al.*, one of ordinary skill in the art would have had to perform *in vitro* enzymatic assays using various substrates with the purified proteins. Thus, as Koeller *et al.* teach that the synthesis of complex carbohydrates, such as heparin, are complicated, and suggest that enzyme-based strategies can be used to greatly simplify glycan assembly, one of ordinary skill in the art would have been motivated to substitute the chemical methods described by Pikas with enzymatic methods, using enzymes such as those described by Habuchi *et al.*. Furthermore, as Pettersson *et al.* and Kobayashi *et al.* provide various conditions for the various enzymatic procedures, one of ordinary skill in the art would have a reasonable expectation of success in substituting the use of *N*-acetylglucosaminyl deacetylase/*N*-deacetylase and sulfotransferase enzymes for the chemical steps disclosed by Pikas. Moreover, although Applicants' argue that the reaction conditions must be carefully selected in order for each step to work, thereby suggesting this feature as a critical element, the rejected claim limitations do not recite these features. Although the claims

are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Applicants further argue that neither Kobayashi *et al.* nor Pettersson *et al.* use a hexasaccharide to generate a defined anticoagulant structure. Moreover, Applicants argue that none of the cited references have used the C5-epimerase and 2-OST enzyme together, and a person skilled in the art would not use the teachings of the references to come up with Applicants' invention that uses more than one enzyme together to produce an oligosaccharide product that can bind to ATIII. Applicants' arguments have been carefully considered but are not found persuasive. Although Applicants claim that neither Kobayashi *et al.* nor Pettersson *et al.* use a hexasaccharide to generate a defined anticoagulant structure, Applicants are requested to not that the rejected claims are drawn only to "a sulfated polysaccharide capable of binding to a protein" or "heparan sulfate." The hexasaccharide and defined anticoagulant structure of Applicants' arguments is not a feature of the rejected claim limitations. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). With regards to Applicants' arguments that none of the cited references teach the use of more than one enzyme together to produce an oligosaccharide product, Koeller *et al.* and Toone *et al.* disclose the advantages of enzymatic synthesis over chemical synthesis. Thus, it would have been *prima facie* obvious for one of ordinary skill in the art to substitute an enzyme for any

chemical reagent in any multi-step synthetic sequence. Furthermore, as Habuchi *et al.* teach that 2-OST typically transfers a sulfate group to the 2-position of iduronic acid, it would have been *prima facie* obvious for one of ordinary skill in the art to couple a synthetic reaction with a C5-epimerase enzyme to convert glucuronic acid to iduronic acid so that the substrate could be sulfated with a 2-OST.

The rejection is still deemed proper and therefore maintained.

Section [0002]

Claims 43 and 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over journal publication by Pikas (IDS dated 26 December 2006), in view of journal article publication by Habuchi *et al.* (of record), in view of journal article publication by Koeller *et al.* (of record), in view of journal article publication by Toone *et al.* (of record), in view of journal article publication by Pettersson *et al.* (of record), in view of journal article publication by Kobayashi *et al.* (of record), as applied to claims 1, 2, 8, 10-18, 20, 22-31, 46, 47 and 67-70, further in view of journal article publication by van Boeckel *et al.* (of record), in view of journal article publication by Kushe *et al.* (of record), in view of journal article publication by Nader *et al.* (of record), in view of journal article publication by Myette *et al.* (of record).

The teachings of Pikas, Habuchi *et al.*, Koeller *et al.*, Toone *et al.*, Pettersson *et al.*, and Kobayashi *et al.*, were as disclosed in section [0001] above of the claim rejections under 35 USC § 103.

The combined teachings of Pikas, Habuchi *et al.*, Koeller *et al.*, Toone *et al.*, Pettersson *et al.*, and Kobayashi *et al.*, differ from that of the instantly claimed invention in that the combined teachings of the prior art do not disclose the use of heparitinase or $\Delta^{4,5}$ unsaturated glycuronidase in the synthesis of heparan sulfate compounds.

Van Boeckel *et al.* teach the unique antithrombin III binding domain of heparin is a lead to new synthetic antithrombotics. Since the ability of heparin fragments to reinforce ATIII-mediated inhibition of factor Xa appeared independent of their size, it was logical to look for the smallest fragments able to catalyze inhibition of factor Xa (p. 1673, column 2, section 2.2). An evaluation of different heparin sulfate fragments suggested that the pentasaccharide sequence DEFGH (Figure 1, p. 1672) is the active sequence (p. 1673, column 2, section 2.2). Van Boeckel *et al.* teach that since no biochemical tool for further controlled degradation was available at the time to obtain pentasaccharide DEFGH from CDEFGH (structure 4 of Figure 1, p. 1672), chemical synthesis was required (p. 1674, column 1, first full paragraph).

Kusche *et al.* teach the biosynthesis of heparin. Extensive studies have elucidated the sequence of events occurring during the biosynthesis of heparin and heparan sulfate (p. 7401, column 1, first incomplete paragraph). In the presence of UDP-GlcNAc and UDP-GlcA, a nonsulfated polysaccharide ((GlcA-GlcNAc)$_n$) is formed that is covalently linked to a protein core in a proteoglycan structure. Upon addition of the sulfate donor PAPS, a series of modifications take place, beginning with deacetylation and N-sulfation of the GlcNAc units. The latter reaction creates the proper substrate structure for C-5 epimerization of GlcA to IdoA units, and the assembly

process is then concluded by stepwise O-sulfation in several positions (C-2 of IdoA and C-2 or C-3 of GlcA units, C-3 and C-6 of GlcN units). The polysaccharide chains of heparin and heparan sulfate display extensive structural variability, with potential for specific interaction with other macromolecules via the presence of unique sequences (p. 7400, column 2, paragraph 1). One such interaction is the antithrombin-binding region, essential for the blood anticoagulant activity of heparin. The structure of the antithrombin-binding region is shown in Figure 1 (p. 7401, column 1). Kushe *et al.* further teach the various substituents of heparin that are important for antithrombin binding. The structure of the pentasacharide sequence is largely nonvariable and cannot be modified without dramatic loss of biological activity (p. 7400, column 2, paragraph 1). As indicated, the 3-*O*-sulfate group of unit III is essential for the high affinity binding of heparin to antithrombin and is a marker component of the antithrombin-binding region (Fig. 1 legend). The 6-*O*-sulfate group of unit I and the N-sulfate groups of units III and V are also critically important for antithrombin binding. The modification of the amino group of unit I with either an acetate or sulfate group does not affect antithrombin binding. Additionally, the sulfate groups at C-2 and C-6 of units IV and V, respectively, are less essential for antithrombin binding.

Nader *et al.* teach the purification and substrate specificity of heparitinase I and heparitinase II from *Flavobacterium heparinum*. These enzymes are responsible for the degradation of glycosaminoglycans. Heparitinase I acts on *N*-acetylated or *N*-sulfated glucosaminido-glucuronic acid linkages of heparan sulfate (abstract). Heparitinase II

acts preferentially upon *N*-6-sulfated and/or *N*-acetylated, 6-sulfated glucosaminido-α-1,4-glucuronic acid linkages (p. 16813, column 1, last paragraph).

Myette *et al.* teach the cloning and substrate specificity of the heparin/heparan sulfate $\Delta^{4,5}$ unsaturated glycuronidase from *Flavobacterium heparinum*. This enzyme hydrolyzes the unsaturated $\Delta^{4,5}$ uronic acid at the nonreducing end of oligosaccharides that result from prior heparinase (and heparitinase) eliminative cleavage (abstract). It discriminates both on the basis of glycosidic linkage and sulfation pattern (abstract).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Pikas, concerning the modification of a polysaccharide having the structure $(GlcA\beta1\text{-}4GlcNAc\alpha1\text{-}4)_n$ by chemical *N*-deacetylation and *N*-sulfation, enzymatic GlcA C5-epimerization, and chemical *O*-sulfation, with the teachings of Habuchi *et al.*, regarding the availability and substrate specificity of the different enzymes involved in the biosynthesis of heparan sulfate, with the teachings of Koeller *et al.*, regarding the use of carbohydrate enzymes as a tool for synthesis of complex carbohydrates, with the teachings of Toone *et al.* regarding enzymes as catalysts in carbohydrate synthesis, with the teachings of Pettersson *et al.*, regarding the purification of a mouse mastocytoma protein required for glucosaminyl *N*-deacetylation and *N*-sulfation, with the teachings of Kobayashi *et al.*, regarding the purification and characterization of a heparan sulfate 2-sulfotransferase from CHO cells, with the teachings of van Boeckel *et al.*, regarding the synthesis of the pentasaccharide sequence DEFGH as an antithrombotic, with the teachings of Kusche *et al.*, regarding the sequence of events involved in the biosynthesis of heparin and heparan sulfate and

the various substituents of heparin that are important for antithrombin binding, with the teachings of Nader *et al.*, regarding heparitinase enzymes which are responsible for the degradation of glycosaminoglycans, with the teachings of Myette *et al.*, regarding the substrate specificity of the heparin/heparan sulfate $\Delta^{4,5}$ unsaturated glycuronidase.

Since van Boeckel *et al.* teach that the pentasaccharide sequence DEFGH is the smallest fragment able to catalyze inhibition of factor Xa and may therefore be useful as an antithrombotic, and Kusche *et al.* teach the importance of the various substituents on the pentasaccharide that are important for antithrombin binding, one of ordinary skill in the art would have been motivated to degrade the polysaccharide chain obtained from *E. coli* K5, as disclosed in Pikas *et al.*, into smaller fragments, more specifically, into the pentasaccharide disclosed by van Boeckel *et al.* and Kusche *et al.* as having antithrombin III activity. As the teachings of Koeller *et al.* and Toone *et al.* indicate that modification and/or synthesis of carbohydrates are advantageously accomplished by the use of enzymes, one of ordinary skill in the art would have been motivated to look to the different enzymes that could be used in the synthesis of the pentasaccharide fragment. As Toone *et al.* teach that enzymes have chemospecificity, regiospecificity, and stereospecificity, and Kusche *et al.* teach the biosynthetic sequence of events for the synthesis of heparin and heparan sulfate, one of ordinary skill in the art would have been motivated to model their order of enzymatic synthetic reactions after the biosynthetic pathway, in order to receive the expected benefit that following the biosynthetic sequence would maintain the specificities of the enzymes. However, as the K5 polysaccharide must also be degraded into the pentasaccharide fragment, one

of ordinary skill in the art would also have to take into account the substrate specificities of these additional enzymes and insert them appropriately into the reaction scheme so as to maintain specificity of all the enzymes necessary for conversion of the *E. coli* K5 polysaccharide, disclosed by Pikas, into the pentasaccharide sequence disclosed by Kusche *et al.* Since the enzyme specificities for heparitinase, used for degradation of the large polymer into smaller saccharide units, is disclosed by Nader *et al.*, and the enzyme specificities of heparin/heparan sulfate $\Delta^{4,5}$ unsaturated glycuronidase, used for removal of the $\Delta^{4,5}$ unsaturated glycosyl residue resulting from heparitinase digestion, is disclosed by Myette *et al.*, it would have been *prima facie* obvious for one of ordinary skill in the art to insert their use appropriately into the heparin/heparan sulfate reaction scheme depending on the required substrate specificities of these additional enzymes.

Thus, as the combined teachings of the prior art teach that pentasaccharide DEFGH, as disclosed by van Boeckel *et al.* and Kusche *et al.*, may be useful as an antithrombotic, one of ordinary skill in the art would have been motivated to synthesize such a compound. Since Koeller *et al.* and Toone *et al.* teach that enzymatic reactions of carbohydrates are advantageous over traditional chemical synthetic methods, one of ordinary skill in the art would have been motivated to identify enzymes useful in the synthesis of heparin/heparin sulfate. As Kushe *et al.* disclose the biosynthetic scheme for the synthesis of heparin/heparin sulfate, and the purified enzymes are readily available and their substrate specificities are known, as taught by Habuchi *et al.*, Pettersson *et al.*, Kobayashi *et al.*, Nader *et al.* and Myette *et al.*, it would have been *prima facie* obvious for one of ordinary skill in the art to use these enzymes, in

accordance with their known substrate specificities, to enzymatically synthesize the pentasaccharide sequence disclosed by van Boeckel *et al.* and Kusche *et al.* as having antithrombotic activity. It is noted that several different enzymatic synthetic sequences could result even after taking into account the different substrate specificities of the individual enzymes involved. However, Applicants are requested to note that it has been held that merely reversing the order of steps in a multi-step process is not a patentable modification absent unexpected or unobvious results. See MPEP § 2144.04. *Ex parte Rubin*, 128 USPQ 440 (Bd. App. 1959); *In re Burhans*, 154 F.2d 690, 69 USPQ 330 (CCPA 1946); *In re Gibson*, 39 F.2d 975, 5 USPQ 230 (CCPA 1930); *Cohn v. Comr. Patents*, 251 F. Supp. 437, 148 USPQ 486 (D.C. 1966).

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

Response to Arguments

Applicants' arguments, filed 26 January 2011, with respect to the rejection of claims 43 and 48 made under 35 USC § 103(a) as being unpatentable over journal article publication by Pikas, in view of journal article publication by Habuchi *et al.*, in view of journal article publication by Koeller *et al.*, in view of journal article publication by Toone *et al.*, in view of journal article publication by Pettersson *et al.*, in view of journal article publication by and Kobayashi *et al.*, as applied to claims 1, 2, 8, 10-18, 20, 22-31, 46, 47 and 67-70, further in view of journal article publication by van Boeckel *et al.*, in view of journal article publication by Kusche *et al.*, in view of journal article publication

by Nader *et al.*, in view of journal article publication by Myette *et al.*, have been fully considered but are not persuasive.

Applicants argue that claims 43 and 48 depend from and incorporate the limitations of claim 1, and since claim 1 is not rendered obvious over Pikas, Habuchi *et al.*, Koeller *et al.* and Toone *et al.*, Pettersson *et al.*, and Kobayashi *et al.*, claims 43 and 48 are also not rendered obvious by the cited publications. As discussed in the "Response to Arguments" heading in section [0001] above, the combined teachings of Pikas, Habuchi *et al.*, Koeller *et al.*, Toone *et al.*, Pettersson *et al.*, and Kobayashi *et al.*, sufficiently render the instantly claimed invention of the independent claims *prima facie* obvious. Thus, the additional teachings of van Boeckel *et al.*, Kusche *et al.*, Nader *et al.* and Myette *et al.* are sufficient to show why one of ordinary skill in the art would include the additional use of heparitinase or $\Delta^{4,5}$ unsaturated glycuronidase in the synthesis of heparan sulfate compounds.

Applicants further argue that van Boeckel *et al.* do not teach nor disclose enzymatic synthesis using the combination of specific isoforms and sizes to generate ATIII binding sequences/structures, and that the targets taught by van Boeckel *et al.* are different than the target disclosed in Applicants' invention. Applicants' arguments have been carefully considered but are not persuasive. The rejection is based on the combined teachings of the prior art. Thus, although van Boeckel *et al.* do not teach the use of enzymatic synthesis to prepare their target, Koehler *et al.* and Toone *et al.* provide one of ordinary skill in the art the motivation to use enzymes rather than chemical reagents by teaching the advantages of enzymatic synthesis for

carbohydrates. With regards to Applicants' argument that van Boeckel *et al.* teach a target different from that disclosed in Applicants' invention, Applicants are requested to note that the rejected claims merely recite a target that is "a sulfated polysaccharide capable of binding to a protein" or "heparan sulfate." Thus, the synthetic target of the claim limitations is met.

Applicants also argue that although Kusche *et al.* teach the use of a pentasaccharide, they fail to teach the use of specific enzymes and further fail to indicate which enzyme acts on which site within the pentasaccharide. Applicants' arguments have been carefully considered but are not persuasive. The rejection is based on the combined teachings of the prior art. Thus, although Kusche *et al.* do not teach the use of enzymatic synthesis to prepare their target, Koehler *et al.* and Toone *et al.* provide one of ordinary skill in the art the motivation to use enzymes rather than chemical reagents by teaching the advantages of enzymatic synthesis for carbohydrates. Additionally, although Kusche *et al.* do not teach which enzyme acts on which site within the pentasaccharide, one of ordinary skill in the art would have this information available to them form the teachings of Habuchi *et al.*, Pettersson *et al.* and Kobayashi *et al.*, which teach the substrate specificity of the different enzymes.

Applicants additionally argue that Nader *et al.* do not teach nor disclose the generation of oligosaccharides, which is in contrast to Applicants' invention directed to the generation of specific, size-defined oligosaccharides that were subjected to enzymatic modification to synthesize/construct ATIII binding domains. Applicants' arguments have been carefully considered but are not persuasive because the rejected

claims are not drawn to a particular size-defined oligosaccharide as argued by Applicants. The rejected claims merely recite a target that is "a sulfated polysaccharide capable of binding to a protein" or "heparan sulfate." Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Applicants further argue that Myette *et al.* only disclose disaccharides and fail to demonstrate that the Δ-4,5-glycouronidase could act on the oligosaccharide structure used in Applicants' invention. However, contrary to Applicants' arguments, the claims are not drawn to a particular oligosaccharide structure, but rather, only to "a sulfated polysaccharide capable of binding to a protein" or "heparan sulfate." Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Furthermore, it is *prima facie* obvious to one of ordinary skill in the art that characterization of an enzyme's specificity is generally performed using the smallest acceptable fragment for ease in manipulation and data interpretation.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art, as described in the new/modified grounds of rejection above.

Section [0003]

Claims 63, 66 and 71 are rejected under 35 U.S.C. 103(a) as being unpatentable over journal article publication by van Boeckel *et al.* (of record), in view of journal article publication by Kushe *et al.* (of record), in view of journal article publication by Pikas (IDS

dated 26 December 2006), in view of journal article publication by Habuchi *et al.* (of record), in view of journal article publication by Nader *et al.* (of record), in view of journal article publication by Myette *et al.* (of record), in view of journal article publication by Koeller *et al.* (of record), in view of journal article publication by Toone *et al.* (of record).

The teachings of van Boeckel *et al.* were as disclosed above in section [0002] of the claim rejections under 35 USC § 103.

The teachings of van Boeckel *et al.* differ from that of the instantly claimed invention in that van Boeckel *et al.* do not disclose synthesis of the ATIII-binding pentsaccharide by enzymatic methods.

The teachings of Kusche *et al.* were as disclosed above in section [0002] of the claim rejections under 35 USC § 103. The structure of Figure 1 wherein R" of unit 1 is an acetate group, R' of unit III is a sulfate group, and the sulfate group at C-6 of unit V is a hydroxyl group, is the same as pentasaccharide (15) of instant claim 66.

The teachings of Pikas were as disclosed in section [0001] above of the claim rejections under 35 USC § 103.

The teachings of Habuchi *et al.* were as disclosed above in section [0001] of the claim rejections under 35 USC § 103.

The teachings of Nader *et al.* were as disclosed in section [0002] above of the claim rejections under 35 USC § 103.

The teachings of Myette *et al.* were as disclosed above in section [0002] of the claim rejections under 35 USC § 103.

The teachings of Koeller *et al.* were as disclosed above in section [0001] of the claim rejections under 35 USC § 103.

The teachings of Toone *et al.* were as disclosed above in section [0001] of the claim rejections under 35 USC § 103.

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of van Boeckel *et al.*, concerning the synthesis of the pentasaccharide sequence DEFGH as an antithrombotic, with the teachings of Kusche *et al.*, regarding the sequence of events involved in the biosynthesis of heparin and heparan sulfate and the various substituents of heparin that are important for antithrombin binding, with the teachings of Pikas, concerning the modification of a polysaccharide having the structure $(GlcA\beta1\text{-}4GlcNAc\alpha1\text{-}4)_n$ by chemical *N*-deacetylation and *N*-sulfation, enzymatic GlcA C5-epimerization, and chemical *O*-sulfation, with the teachings of Habuchi *et al.*, regarding the availability and substrate specificity of the different enzymes involved in the biosynthesis of heparan sulfate, with the teachings of Nader *et al.*, regarding heparitinase enzymes which are responsible for the degradation of glycosaminoglycans, with the teachings of Myette *et al.*, regarding the substrate specificity of the heparin/heparan sulfate $\Delta^{4,5}$ unsaturated glycuronidase, with the teachings of Koeller *et al.*, regarding the use of carbohydrate enzymes as a tool for synthesis of complex carbohydrates, with the teachings of Toone *et al.* regarding enzymes as catalysts in carbohydrate synthesis.

Since van Boeckel *et al.* teach that the pentasaccharide sequence DEFGH is the smallest fragment able to catalyze inhibition of factor Xa and may therefore be useful as

an antithrombotic, and Kusche *et al.* teach the importance of the various substituents on the pentasaccharide that are important for antithrombin binding, one of ordinary skill in the art would have been motivated to degrade the polysaccharide chain obtained from *E. coli* K5, as disclosed in Pikas *et al.*, into smaller fragments, more specifically, into the pentasaccharide disclosed by van Boeckel *et al.* and Kusche *et al.* as having antithrombin III activity. As the teachings of Koeller *et al.* and Toone *et al.* indicate that modification and/or synthesis of carbohydrates are advantageously accomplished by the use of enzymes, one of ordinary skill in the art would have been motivated to look to the different enzymes that could be used in the synthesis of the pentasaccharide fragment. As Toone *et al.* teach that enzymes have chemospecificity, regiospecificity, and stereospecificity, and Kusche *et al.* teach the biosynthetic sequence of events for the synthesis of heparin and heparan sulfate, one of ordinary skill in the art would have been motivated to model their order of enzymatic synthetic reactions after the biosynthetic pathway, in order to receive the expected benefit that following the biosynthetic sequence would maintain the specificities of the enzymes. However, as the K5 polysaccharide must also be degraded into the pentasaccharide fragment, one of ordinary skill in the art would also have to take into account the substrate specificities of these additional enzymes and insert them appropriately into the reaction scheme so as to maintain specificity of all the enzymes necessary for conversion of the *E. coli* K5 polysaccharide, disclosed by Pikas, into the pentasaccharide sequence disclosed by Kusche *et al.* Since the enzyme specificities for heparitinase, used for degradation of the large polymer into smaller saccharide units, is disclosed by Nader *et al.*, and the

enzyme specificities of heparin/heparan sulfate $\Delta^{4,5}$ unsaturated glycuronidase, used for removal of the $\Delta^{4,5}$ unsaturated glycosyl residue resulting from heparitinase digestion, is disclosed by Myette *et al.*, it would have been *prima facie* obvious for one of ordinary skill in the art to insert their use appropriately into the heparin/heparan sulfate reaction scheme depending on the required substrate specificities of these additional enzymes. More specifically, as Nader *et al.* teach that heparitinase I acts on *N*-acetylated or *N*-sulfated glucosaminido-glucuronic acid linkages of heparan sulfate, one of ordinary skill in the art would have been motivated to insert the use of this enzyme after *N*-deacetylase/*N*-sulfotransferase of the *E. coli* K5 polysaccharide. Another advantage of degrading the polysaccharide early in the synthetic scheme is that smaller fragments are more easily manipulated and characterized than larger structures. With regards to the heparin/heparan sulfate $\Delta^{4,5}$ unsaturated glycuronidase, as Myette *et al.* teach that this enzyme hydrolyzes the unsaturated $\Delta^{4,5}$ uronic acid at the nonreducing end of oligosaccharides that result from prior heparinase (and heparitinase) eliminative cleavage, one of ordinary skill in the art would have been motivated to insert the use of this enzyme at a point after degradation of the polysaccharide by heparitinase I.

Thus, as the combined teachings of the prior art teach that pentasaccharide DEFGH, as disclosed by van Boeckel *et al.* and Kusche *et al.*, and which is the same as pentasaccharide (15) of the instantly claimed methods, may be useful as an antithrombotic, one of ordinary skill in the art would have been motivated to synthesize such a compound. Since Koeller *et al.* and Toone *et al.* teach that enzymatic reactions of carbohydrates are advantageous over traditional chemical synthetic methods, one of

ordinary skill in the art would have been motivated to identify enzymes useful in the synthesis of heparin/heparin sulfate. As Kushe *et al.* disclose the biosynthetic scheme for the synthesis of heparin/heparin sulfate, and the purified enzymes are readily available and their substrate specificities are known, as taught by Habuchi *et al.*, Nader *et al.* and Myette *et al.*, it would have been *prima facie* obvious for one of ordinary skill in the art to use these enzymes, in accordance with their known substrate specificities, to enzymatically synthesize the pentasaccharide sequence disclosed by van Boeckel *et al.* and Kusche *et al.* as having antithrombotic activity. It is noted that several different enzymatic synthetic sequences could result even after taking into account the different substrate specificities of the individual enzymes involved. However, Applicants are requested to note that it has been held that merely reversing the order of steps in a multi-step process is not a patentable modification absent unexpected or unobvious results. See MPEP § 2144.04. *Ex parte Rubin*, 128 USPQ 440 (Bd. App. 1959); *In re Burhans*, 154 F.2d 690, 69 USPQ 330 (CCPA 1946); *In re Gibson*, 39 F.2d 975, 5 USPQ 230 (CCPA 1930); *Cohn v. Comr. Patents*, 251 F. Supp. 437, 148 USPQ 486 (D.C. 1966).

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

Response to Arguments

Applicants' arguments, filed 26 January 2011, with respect to the rejection of claims 63, 66 and 71 made under 35 USC § 103(a) as being unpatentable over journal

article publication by van Boeckel *et al.*, in view of journal article publication by Kushe *et al.*, in view of journal article publication by Pikas, in view of journal article publication by Habuchi *et al.*, in view of journal article publication by Nader *et al.*, in view of journal article publication by Myette *et al.*, in view of journal article publication by Koeller *et al.*, in view of journal article publication by Toone *et al.*, have been fully considered but they are not persuasive.

In each of the arguments, Applicants' only argue how each prior art, specifically, van Boeckel *et al.*, Kusche *et al.*, Pikas, Habuchi *et al.*, Koeller *et al.*, Toone *et al.*, Nader *et al.* and Myette *et al.* do not teach a particular aspect of the instantly claimed invention, thereby concluding that the van Boeckel, in view of Kusche *et al.*, in view of Pikas, in view of Habuchi *et al.*, in view of Nader *et al.*, in view of Myette *et al.*, in view of Koeller *et al.*, in view of Toone *et al.* do not disclose a stepwise, enzymatic *in vitro* sulfation process that consists of the epimerases and O-sulfotransferases of the present invention. Applicants' arguments have been carefully considered but are not found persuasive. Applicants are requested to note that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Furthermore, one cannot merely conclude that the combined teachings of the art does not teach the instantly claimed invention by arguing what feature is not taught in each of the cited prior art references. One of ordinary skill in the art must look at the features that are taught and whether or

not it would have been obvious to combine the various features of the prior art to arrive at the instantly claimed invention.

In the instant rejection, the combined teachings of the prior art teach that pentasaccharide DEFGH, as disclosed by van Boeckel *et al.* and Kusche *et al.*, and which is the same as pentasaccharide (15) of the instantly claimed methods, may be useful as an antithrombotic, thereby providing motivation to one of ordinary skill in the art to synthesize such a compound. Although Applicants argue that the van Boeckel *et al.* oligosaccharide differs from pentasaccharide 15 of the instant claims, Applicants' are requested to note Kusche *et al.* disclose key features of the anti-thrombin site that are important for binding. Thus, one of ordinary skill in the art would know which positions can be modified and what modifications are acceptable. Furthermore, since Koeller *et al.* and Toone *et al.* teach that enzymatic reactions of carbohydrates are advantageous over traditional chemical synthetic methods, one of ordinary skill in the art would have been motivated to identify enzymes useful in the synthesis of heparin/heparin sulfate. As Kushe *et al.* disclose the biosynthetic scheme for the synthesis of heparin/heparin sulfate, and the purified enzymes are readily available and their substrate specificities are known, as taught by Habuchi *et al.*, Nader *et al.* and Myette *et al.*, it would have been *prima facie* obvious for one of ordinary skill in the art to use these enzymes, in accordance with their known substrate specificities, to enzymatically synthesize the pentasaccharide sequence disclosed by van Boeckel *et al.* and Kusche *et al.* as having antithrombotic activity. It is noted that several different enzymatic synthetic sequences could result even after taking into account the different substrate specificities of the

individual enzymes involved. However, Applicants are requested to note that it has been held that merely reversing the order of steps in a multi-step process is not a patentable modification absent unexpected or unobvious results. See MPEP § 2144.04. *Ex parte Rubin*, 128 USPQ 440 (Bd. App. 1959); *In re Burhans*, 154 F.2d 690, 69 USPQ 330 (CCPA 1946); *In re Gibson*, 39 F.2d 975, 5 USPQ 230 (CCPA 1930); *Cohn v. Comr. Patents*, 251 F. Supp. 437, 148 USPQ 486 (D.C. 1966). Furthermore,it has been held that "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR*, 550 U.S. at ___, 82 USPQ2d at 1395. With respect to the teachings of the prior art, pentasaccharide 15 and hexasaccharide 11 are obvious in view of the teachings of the prior art. Furthermore, enzymes for the modification of sulfated polysaccharides are known and have been cloned in the prior art, along with characterization of their substrate specificities. Thus, one of ordinary skill in the art would expect that a combination of the known enzymatic methods to synthesize an obvious compound would yield a predictable result.

The rejection is still deemed proper and therefore maintained.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.
Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 2, 8, 10, 14 and 16 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 16-26 of copending application no. 10/473,180.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application is drawn to an in vitro method of enriching the portion of anticoagulant active heparin sulfate present in a polysaccharide preparation comprising providing a 3-O-sulfated polysaccharide preparation, and contacting the preparation with a 6-OST protein in the presence of a sulfate donor (claim 16). The 3-O-sulfated polysaccharide preparation is made in a CHO cell (claim 17).

The claims of the instant application are drawn to a method of preparing a sulfated polysaccharide or heparan sulfate comprising treating an unsulfated or incompletely sulfated polysaccharide or unsulfated heparan synthon with at least one enzyme (claims 1, 2, 8 and 10). The enzyme is selected from the group consisting of an *N*-deacetylase, an *N*-sulfotransferase, an epimerase and an *O*-sulfotransferase (claim 6). The unsulfated polysaccharide is isolated from a cell (claim 14).

Thus, the instant claims 1, 2, 8, 10, 14 and 16 are seen to be anticipated by claims 16-26 of copending application no. 10/473,180.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1, 2, 8, 10-13, 18, 20, 22-24 and 26-30 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 13, 18, 19, 24, 29 and 30 of copending application no. 11/204,391.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application is drawn to a method for the preparation of *N*-sulfate derivatives of non-sulfated *N*-acetyl heparosan polysaccharides comprising the steps of (a) contacting a non-sulfated *N*-acetyl heparosan polysaccharide witn *N*-deacetylase-*N*-sulfotransferase and glucuronosyl C-5 epimerase to generate an iduronic acid-enriched polysaccharide; (b) contacting the product in (a) with 6-*O*-sulfotransferase and 3-*O*-sulfotransferase; and (c) isolating the product of (b) which yields N-deacetylated N-sulfate derivatives of non-sulfated N-acetyl heparosan (claims 13 and 24). The 3-*O*-sulfotransferase is 3-OST1, 3-OST2, 3-OST3, 3-OST4 or 3-OST5 (claims 18 and 29). The 6-*O*-sulfotransferase is 6-OST1, 6-OST2 or 6-OST3 (claims 19 and 30).

The claims of the instant application are drawn to a method of preparing a sulfated polysaccharide or heparan sulfate comprising treating an unsulfated or incompletely sulfated polysaccharide or unsulfated heparan synthon with at least one enzyme (claims 1, 2, 8 and 10). The enzyme is selected from the group consisting of

an *N*-deacetylase, an *N*-sulfotransferase, an epimerase and an *O*-sulfotransferase (claim 6). The method comprises (a) treating an unsulfated polysaccharide with an N-deacetylating reagent; (b) treating the step (a) product with an *N*-sulfating reagent; (c) treating the step (b) product with an epimerizing reagent; and (d) treating the step (c) product with at least one *O*-sulfating reagent (claims 11 and 12). The heparan synthon is a non-sulfated *N*-acetyl heparosan (claim 13). The deacetylating reagent is selected from the group consisting of a deacetylase and *N*-deacetylase-*N*-sulfotransferase (claims 18 and 20). The epimerizing reagent is selected from the group consisting of C5-epimerase (claim 22). The *O*-sulfating reagent incorporates a 3-*O*-sulfate group or a 6-*O*-sulfate group (claims 23, 24 and 26). The *O*-sulfating reagent is a 3-*O*-sulfotransferase selected from the group consisting of 3-OST1, 3-OST2, 3-OST3, 3-OST4, 3-OST5 and 3-OST6 (claims 27 and 28). The *O*-sulfating reagent is a 6-O-sulfotransferase selected from the group consisting of 6-OST1, 6-OST2 and 6-OST3 (claims 29 and 30).

Thus, the instant claims 1, 2, 8, 10-13, 18, 20, 22-24 and 26-30 are seen to be anticipated by claims 13, 18, 19, 24, 29 and 30 of copending application no. 11/204,391.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1, 2, 8, 10-18, 20 and 22-31 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 6,

16, 17, 19 and 20 of U.S. Patent No. 7,655,445 (claims refer to U.S. application no. 10/986,058 as the published patent is not immediately available in the database).

Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application is drawn to a method for the synthesis of an epimerically enriched form of a sulfated heparosan polysaccharide, comprising an acceptor heparosan polysaccharide with PAPS, at least one sulfotransferase, a p-nitrophenyl sulfate donor, an arylsulfatase and an epimerase (claim 1). The epimerase is a glucuronosyl C5 epimerase (claim 6). The sulfated heparosan is isolated (claims 16). The sulfotransferase is an *N*-deacetylase-*N*-sulfotransferase, heparin sulfate 2-*O*-sulfotransferase, 6-*O*-sulfotransferase, 3-*O*-sulfotransferase, 2-*O*-sulfotransferase, or a combination thereof (claim 17). The 3-*O*-sulfotransferse is 3-OST1 (claim 19). The 6-*O*-sulfotransferase is 6-OST1, 6-OST2 or 6-OST3 (claim 20).

The claims of the instant application are drawn to a method of preparing a sulfated polysaccharide or heparan sulfate comprising treating an unsulfated or incompletely sulfated polysaccharide or unsulfated heparan synthon with at least one enzyme (claims 1, 2, 8 and 10). The enzyme is selected from the group consisting of an *N*-deacetylase, an *N*-sulfotransferase, an epimerase and an *O*-sulfotransferase (claim 6). The method comprises (a) treating an unsulfated polysaccharide with an *N*-deacetylating reagent; (b) treating the step (a) product with an *N*-sulfating reagent; (c) treating the step (b) product with an epimerizing reagent; and (d) treating the step (c) product with at least one *O*-sulfating reagent (claims 11 and 12). The heparan synthon

is a non-sulfated *N*-acetyl heparosan (claim 13). The unsulfated polysaccharide or heparan synthon is isolated from a cell or *E. coli* bacteria (claims 14-17). The deacetylating reagent is selected from the group consisting of a deacetylase and *N*-deacetylase-*N*-sulfotransferase (claims 18 and 20). The epimerizing reagent is selected from the group consisting of C5-epimerase (claim 22). The *O*-sulfating reagent incorporates a 2-*O*-sulfate group, 3-*O*-sulfate group or a 6-*O*-sulfate group (claims 23-26). The *O*-sulfating reagent is a 3-*O*-sulfotransferase selected from the group consisting of 3-OST1, 3-OST2, 3-OST3, 3-OST4, 3-OST5 and 3-OST6 (claims 27 and 28). The *O*-sulfating reagent is a 6-*O*-sulfotransferase selected from the group consisting of 6-OST1, 6-OST2 and 6-OST3 (claims 29 and 30). The *O*-sulfating reagent is a 2-*O*-sulfotransferase (claim 31).

Thus, the instant claims 1, 2, 8, 10-18, 20 and 22-31 are seen to be anticipated by claims 1, 6, 16, 17, 19 and 20 of copending application no. 10/986,058, now U.S. Patent No. 7,655,445.

Response to Arguments

Applicants' intent that a terminal disclaimer will be filed over the copending applications or patents upon indication of allowable subject matter, in the reply filed on 26 January 2011, is acknowledged.

The rejections are still deemed proper and therefore maintained.

Conclusion

In view of the rejections to the pending claims set forth above, no claim is allowed.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SCARLETT GOON whose telephone number is

(571)270-5241. The examiner can normally be reached on Mon - Thu 7:00 am - 4 pm and every other Fri 7:00 am - 12 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Shaojia Anna Jiang/
Supervisory Patent Examiner, Art Unit 1623

/SCARLETT GOON/
Examiner
Art Unit 1623